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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	6

DATE MAILED: 12/05/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/654,293	CHRISTMANN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-27 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to cloned avian, methods of producing cloned avians, methods of producing cloned non-human animals and methods of producing a protein from the cloned avians.

The specification methods of cloning non-human animals, and in particular, avian, by nuclear transfer. In particular, the specification teaches that nuclear transfer in avians has been difficult to realize because of the inaccessibility of the early avian egg (see p. 6, lines 11-20). The specification teaches that the hen oviduct offers potential as a protein bioreactor, however, efforts to produce transgenic chickens by microinjection has been unpredictable (see p. 7, lines 1-18). The specification teaches that two-photon laser scanning microscopy (TPLSM) would be used to visualize nuclear structures in the recipient cell in nuclear transfer, because the cell is enucleated (see p.

10, line 3-15). The specification teaches that ova were isolated from hens 2-4 hours after oviposition of the previous egg. These eggs were then prepared for visualization by TPLSM and the pronuclear structures were ablated by laser-mediated ablation. (See Example 1). The donor nucleus was isolated from fibroblast cells (Example 2). The reconstructed zygote was then prepared by a micromanipulation unit which allowed the injection of the somatic cells in the germinal disk of the enucleated ova (Example 3). The specification teaches that these ova can then be transferred into recipient hens, which can then lay the eggs (Example 4).

However, the specification does not provide sufficient teaching or guidance to show that such that all cloned non-human animals, or in particular avian, could be produced by nuclear transfer. Numerous factors influence the probability of producing an animal by cloning, and with particularity, the species of the animal. Westhusin *et al.* (**Theriogenology**, Vol. 55, pp. 35-49, 2001) review the state of the art of cloning. They state that, "Without a doubt, one of the major factors influencing the probability of cloning a specific animal is species. While the basic approach involving nuclear transfer may be similar, the specific materials and methods utilized for cloning one species of animal do not automatically apply across different species." (see p. 36, 4th paragraph). Westhusin *et al.* further state that the factors to consider when cloning animals by nuclear transfer include acquisition of mature ova, enucleation of mature ova, nuclear transfer into the enucleated ova, activation of the newly formed embryo, culturing the embryo *in vitro* and transferring the embryo into a surrogate mother. Furthermore, these

techniques and the efficacy of these techniques will vary from species to species. (see p. 36-37, bridging paragraph).

Westhusin *et al.* discuss the state of the art of cloning of cattle, sheep, goat, mice and pigs in detail (see pp. 37-39) and particularly state that the production of cloned animals by somatic cell nuclear transfer has only been reported in the species described although there continue to be ongoing experiments in other species of animals (see p. 39, 3rd paragraph). Westhusin *et al.* further discuss other variables that can affect cloning efficiency, such as the type of donor cells used and genetic modifications (see pp. 40-45).

As discussed above, Westhusin *et al.* clearly show the unpredictable state of the art of nuclear transfer with regard to the unpredictable factors such as species difference, donor cells and genetic modifications. As the specification fails to provide any guidance or teaching for the production of any cloned non-human animal or avian, one of skill would not be able to rely upon the state of the nuclear transfer art for an attempt to produce such non-human animals.

Furthermore, the claimed invention is directed to producing cloned non-human animals and in particular, cloned avian. However, the method steps of the claims do not enable the claimed invention, because the claims do not provide a step of transferring the reconstructed zygote into a recipient female to allow the zygote to come to term. It would not be expected that the reconstructed zygote would develop into any non-human animal or bird without this step. Furthermore, it is noted that, with regard to implantation of the reconstructed zygote into a recipient female, the recipient female must be of the

same species as the zygote. This is because implantation of a fetus into two unrelated species is not predictable, as Fehilly *et al.* (**Nature**, Vol. 307, 16 February 1984) teach that often two unrelated species cannot carry a live hybrid fetus to term due to factors such as interspecific pregnancies, placental abnormalities and maternal immunological reaction against foreign antigens of the conceptus which would be the cause of immediate abortion (see p. 634, 1st column, 2nd paragraph). Fehilly *et al.* summarize experiments for the production of such animals, and show an extremely low percentage of full term young (see Table 1, p. 635). Although Fehilly *et al.* show that is possible to produce embryos that have been implanted into surrogate mothers of a foreign species, it is clearly an unpredictable process.

The claimed invention encompasses the use of any recipient cell for use in nuclear transfer. It is noted that it is well-known in the art that recipient cells that are commonly used for nuclear transfers are oocytes arrested at metaphase II, and pronuclear zygotes (see Specification p. 4, lines 19-20). To this end, it would not be predicted that use of any other enucleated recipient cell, other than the above-described, would result in successful nuclear transfer. For example, Kato *et al.* (Theriogenology, 37: 769-778, 1992) attempted to fuse mouse fetal germ cells with enucleated blastomeres of 2-cell embryos. Kato *et al.* used 3 groups of blastomeres, which were obtained at various time points. After fusion, the blastomeres were cultured to examine their developmental capacity (see Abstract). It was found that 2 of the 3 groups of fused blastomeres did not divide, but several from the third group divided (collected at 47-52 hours after treatment with human chorionic gonadotropin), and some

developed into normal blastocysts. These normal blastocysts were then transferred into recipient females and allowed to come to term. It was found that none of the resulting progeny showed any contribution of the donor germ cells. Kato *et al.* teach that the proportion of enucleated blastocysts that developed into normal blastocysts following nuclear transfer was quite low (see p. 777, 2nd paragraph) and state that, "Differences in developmental stages between germ cells and recipient two-cell embryos may have been too large to permit the production of chimeric offspring." (see p. 777, last paragraph). To this end, only enucleated oocytes arrested at MII and pronuclear zygotes could be used for successful nuclear transfer.

The claims are directed to producing a cloned non-human animal or avian via nuclear transfer. However, the method steps do not enable the claimed invention because they do not describe a step of cell-cell fusion. It is well-known in the nuclear transfer art that cell-cell fusion must take place in order to effect nuclear transfer; however, the claims do not provide such a step. To this end, the claimed methods absent the fusion step would not be predicted to result in successful nuclear transfer to produce the claimed cloned non-human animals or avian.

Furthermore, the claimed invention encompasses the production of transgenic non-human animals and avian. It is noted that while gene transfer techniques are well-developed for a number of species, especially in the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of

the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, birds, cows, fish, pigs, etc. that can affect the phenotype in an unpredictable manner. With the lack of working examples provided by the specification, as well as the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic animals.

Therefore, in view of the quantity of experimentation necessary to determine the parameters for nuclear transfer for the production of all species of cloned non-human animals, the lack of direction or working examples provided by the specification for the production of all species of cloned non-human animals, and in particular, cloned avian, the breadth of the claims encompassing the production of all non-human animals, the unpredictable state of the art for the implantation of embryos into surrogate mothers of foreign species, as well as the unpredictable state of the art of nuclear transfer and transgenics, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "about" in claim 3 is a relative term which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 5 recites the limitation "ablation" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the culturing " in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Hughes *et al.* (US Pat No. 4,997,763, published 3/5/1991, Reference A3).

Claim 23 is directed to an intact hard-shell egg containing protein exogenous to the egg.

Hughes *et al.* teach stable vectors that can be used to insert and express foreign genes into somatic avian cells both *in vivo* and *in vitro* (see Abstract). Hughes *et al.* teach that the vector can be injected into multiple ova before ovulation, or binding the vector to sperm with an agent such as DEAE dextran. This sperm would then carry the vector into the ovum and the resulting hard-shell eggs that would be laid would contain the vector expression the exogenous gene(s) (see col. 12, lines 17-42).

Accordingly, Hughes *et al.* anticipate claim 23.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Karen Hauda, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-6608. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Deborah Crouch

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